Small Deletion of 143 Kb Encompassing Exon 2 of the AUTS2: Rise of a New Microdeletion Syndrome?

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Introduction

Chromosome Microarray Analysis is a powerful diagnostic tool and is being used as a first-line approach to detect chromosome imbalances associated with intellectual disability, dysmorphic features and congenital anomalies. This test enables the identification of new copy number variants (CNVs) and their association with new microdeletion/microduplication syndromes in patients previously studied by conventional cytogenetics analysis. Here we report the case of a female with severe intellectual disability, absence of speech, microcephaly and congenital abnormalities with a previous normal karyotype performed at a younger age.

Microarray analysis was performed at 17 years of age, in order to assess if a genome imbalance could explain the patient’s undiagnosed phenotype. A small deletion was found in autism susceptibility candidate 2 (AUTS2) gene.

The AUTS2 gene has been recently implicated in autism disorder mental retardation with variable syndromic phenotype (OMIM *607720, *615834). Common clinical features described in patients with deletions in AUTS2 gene include autism, intellectual disability, speech delay and microcephaly, among others 1-4,6,8,9,10,11,12,13,14,15,16.

We compare our patient with similar reported cases, adding additional value to the phenotype-genotype correlation of CNVs in this region.

Method

Microarray analysis was carried out in DNA extracted from peripheral blood using Affymetrix CytoScan HD chromosome microarray platform according to the manufacturer’s recommendations. CytoScan HD array provide 750,000 polymorphic (SNP, single nucleotide polymorphism) and 3,000,000 non-polymorphic (CNV). The raw data were processed using Affymetrix Chromosome Analysis Suite software (CHAS) and the output data were interpreted with the UCSC Genome Browser (http://genome.ucsc.edu/ GRCh37/hg38 assemblies), DECIPHER (http://decipher.sanger.ac.uk) and ClinGen (http://clinvar.ncbi.nlm.nih.gov/). The function of the gene, which were located within the region of the genomic imbalance, was retrieved from the GeneCards (http://www.genecards.org/) and OMIM (http://www.ncbi.nlm.nih.gov/omim) databases.

Results and Discussion

A deletion with 143 Kb at the 7q11.22 breakpoint was identified. Parents were not available to assess inheritance for this CNV.

The CNV identified in our patient was classified as of clinical significance, and most likely accounts for the clinical features reported.

At the top of the most frequently reported clinical features, one can easily conclude that in almost all cases (4/5) is present, with the exception of 2/3 cases. Also microcephaly (18/30) and short stature (13/30) are among the clinical features most observed. ASD curiously was only present in 39% of the total number considered here (12/31), despite the name of the gene (autism susceptibility candidate 2).

Considering the exons phenotype distribution, apparently there are a number of large clinical features observed at exon 6. Further investigation would be necessary to assess the eventual higher importance for this particular exon.

Table 1: Comparison of our case (ANSA) with other six published case studies (A – F). The total number of patients included in the table is of 31, although case study C, per se, has 21 of the total.

Table: Clinical features observed per exon

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Conclusion

In summary, the growing collection of new cases with similar clinical features, and the observation of this deletion occurring frequently de novo (in the present cases it occurs with a relative percentage of 71%), indicates the CNV as having a strong likelihood of being associated with a new single gene microdeletion syndrome.

References


